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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,560	04/08/2004	Patrick Midoux	410.015-Reissue	8665

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EXAMINER	
NGUYEN, DAVE TRONG	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,560	MIDOUX ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11-15* is/are allowed.

6)☒ Claim(s) *1-10 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The specification is objected because the first paragraph of the specification regarding the cross-reference information needs to be updated to reflect the relationship between this reissue application and the issued patent

Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

The reissue oath or declaration filed July 12, 2004 complies with 37 CFR 1.63 and with 37 CFR 1.175.

The amendment filed April 8, 2004 proposes amendments to claims 1, 2 and 16 that do not comply with 37 CFR 1.173(b), which sets forth the manner of making amendments in reissue applications. For example, a parenthetical expression "amended," "twice amended," etc., should follow the claim number. In the proposed amendment, the recitation of "(currently amended)" or "(new)" is not correct. Also, the new claim 16 was not entirely underlined. See MEPEP 173(b). For changes to the claims, one must submit a copy of the entire patent claim with the amendments shown by underlining and bracketing.

Pursuant to 37 CFR 1.173(c), each amendment submitted must set forth the status of all patent claims and all added claims as of the date of the submission. The status to be set forth is whether the claim is pending or canceled. The failure to submit the claim status will generally result in a notification to applicant that the amendment prior to final rejection is not completely responsive (see 37 CFR 1.135(c)). Such an amendment after final rejection will not be entered.

Also pursuant to 37 CFR 1.173(c), each claim amendment must be accompanied by an explanation of the support in the disclosure of the patent for the amendment (i.e., support for all changes made in the claim(s), whether insertions or deletions). The failure to submit an explanation will generally result in a notification to applicant that the amendment prior to final rejection is not completely responsive (see 37 CFR 1.135(c)). Such an amendment after final rejection will not be entered.

A supplemental paper correctly amending the reissue application is required.

The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 6,372,499 B1 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation. Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application. These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04

Claims 1-10, and 16 rejected under 35 U.S.C. 251 as being an improper recapture of broadenedclaimed subject matter surrendered in the application for the

patent upon which the present reissue is based. See *Pannu v. Storz Instruments Inc.*, 258 F.3d 1366, 59 USPQ2d 1597 (Fed. Cir. 2001); *Hester Industries, Inc. v. Stein, Inc.*, 142 F.3d 1472, 46 USPQ2d 1641 (Fed. Cir. 1998); *In re Clement*, 131 F.3d 1464, 45 USPQ2d 1161 (Fed. Cir. 1997); *Ball Corp. v. United States*, 729 F.2d 1429, 1436, 221 USPQ 289, 295 (Fed. Cir. 1984). A broadening aspect is present in the reissue which was not present in the application for patent. The record of the application for the patent shows that the broadening aspect (in the reissue) relates to subject matter that applicant previously surrendered during the prosecution of the application. Accordingly, the narrow scope of the claims in the patent was not an error within the meaning of 35 U.S.C. 251, and the broader scope surrendered in the application for the patent cannot be recaptured by the filing of the present reissue application.

The improper recapture of broadened claimed subject matter existes because of the recapturd limitations "compounds having an imidazole nucleus" as recited in claim 1, "histidine" as recited in claim 2, and the "the residue causing destabilization of cell membrane in a weakly acid medium is alkylimidazole" as recited in claim 16.

These specific recited limitatations do relate to claimed emobodiments that applicant previously surrendered during the prosecution of the original application (which became the patent to be reissued). More specifically, the prosecution history of the 09/297,519 (now US pat No. 6,372,499 B1) clearly shows that in response to the final rejection dated July 13, 2001, which has prior art rejections, drawn to specifically to histidine residues, or residues with an imidazole nucleus conjugated to polylysine,

Applicant introduces a claim amendment after final, dated October 11, 2001. This claim amendment after final clearly was rewritten in order to omit the very same limitations that were subjected to the prior art rejections as set forth in the final rejection. In fact, the interview dated July 31, 2001 indicates that should applicant rewrite the claims so as to omit the limitations, drawn to residues with an imidazole nucleus or histidine residues, and to conform according to languages suggested by the examiner in the interview, all of the prior art rejections would be withdrawn. As such and even though applicant made no argument on the record that the limitation was dropped obviate the rejection, the nature of the claims rewritten in the amendment after final can show that the limitation of "compounds with an imidazole nucleus or histidine residues (see claim 27 of the preliminary amendment dated 7/23/99) was deleted in direct reply to the rejection. This action, in view of MPEP 1412.02 will establish the added limitation as relating to subject matter previously surrendered. Note also the reissue claims are not equal in scope to, or narrower than, the claims of the original patent in all aspects. Therefore, with respect to claimed embodiments, specifically drawn to "compounds having an imidazole nucleus" as recited in claim 1, "histidine" as recited in claim 2, and the "the residue causing destabilization of cell membrane in a weakly acid medium is alkylimidazole", there is an improper recapture.

However, should applicant delete the improper recaptured limitations by amending the currently pending claims in a proper format regarding an reissue application, there would be no recapture.

The following grounds of rejection, which were set forth in the final rejection dated October 11, 2001, are applicable to the improper recaptured claimed embodiments.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a)..

Claims 1-10, and 16 are rejected under 35 U.S.C. 103 as being unpatentable over either FR-A-2719316 (D1, cited in the written opinion from PCT officers) or Midoux *et al.* (US Pat No. 5,733,762, 3/1998, wherein Erbacher and Roche-Degremont constitute as another inventive entity, entire document), taken with Wang *et al.* (D3,

Biochemistry, 1984, 23, 4409-4416, also cited in the Written Opinion from PCT officers in the parent application).

D1 and Midoux describe a complex between at least one negatively charged nucleic acid and at least one positively charged polymeric conjugate bonded by electrostatic interaction. The polymeric conjugate contains a polymer of monomeric units with free NH3+ groups. The free NH3+ are substituted, with a ratio of at least 10%, by gluconyl based non-charge residues and do not bind to any recognition signal recognized by a cell membrane receptor (entire documents).

The difference between D1 or Midoux and the subject matter of the present claimed invention is that the claimed invention is directed to histidine residues that are protonable in a weakly acidic medium and further comprise a functional group enabling them to be bound to the polymer while not being recognized by a cell membrane receptor. The objective of employing histidine residues or residues with an imidazole nucleus conjugated to polylysine, for example, is to enhance the protection of transfectinng nucleic acid from lysosomal decomposition following endocytosis.

However, at the time the invention was made, D3 describes the fusion-mediating properties of polyhistidine relative to liposomes. The concept of fusion is caused by the polycationic nature of polyhistidine having an acid pH, and to the combination of the polycation with membrane phospholipids that induces phase separation in the dual lipid layer (D3, abstract). D3 also indicates that the fusion-mediating behavior associated with polyhistidine having a low pH is more effective than the one associated with Ca2+ or polylysine. More specifically, D3 indicates that a charge ratio of only 0.2 or less

between the polyhistidine and the liposome enables effective fusion to be ensured, whereas it must exceed 0.7 with Ca2+ and be of around 1 with polylysine (see page 4414, column 2, last sentence to page 4415, column 1, line 13; table IV). In addition and most importantly, D3 suggests that if the interaction between the hydrophobic segments of viral envelope glycoproteins is an important step in the fusion process, the protonation of the histidine residues of the viral protein with an acidic pH would be an alternative fusion means (page 4115, last paragraph).

It would have been obvious for one of ordinary skill in the art to incorporate histidine residues to any of the free NH3 groups of the polylysine in D1 in order to enhance the fusion and translocation of DNA complexed with polylysine. One of ordinary skill in the art would have been motivated to incorporate histidine residues to any of the free NH3 groups of the polylysine in D1 because of the reasons set forth in the preceding paragraphs.

To the extent that the claims are readable on specific substitution ratios, and further optional incorporation of cell-recognition peptides, it would have been obvious to one of ordinary skill in the art as a matter of design choice to employ any ratio and/or well known cell recognition peptides in the polymeric complexes of D1 taken with D3, particularly since such teachings are also disclosed in D1 (claims 1 and 4) and in Midoux *et al.*

To the extent that the claim are readable on residues belonging to the family of compounds that comprise an imidazole ring, having residues that are alkylimidazoles, the claims are directed to minor modification and/or obvious variants of the polymeric

complexes, and one of ordinary skill in the art would have been motivated as a matter of design choice to employ these well-known compounds as obvious variants of histidines, particularly since D1 teaches that the polymer includes a grouping of formula (I) and (II) (see D1, claims 6 and 8). Likewise, the selection of recognition signals, the selection of nucleic acids and the selection of the defining parameters of the polymer, *e.g.,* the substitution ratio of the free NH3+ of the lysine units, the selection of the molecular weight of the nuclei acid and the average number of base pairs of the nucleic acid per monomeric unit molecule, are minor modification or options that a person of ordinary skill in the art would have been motivated to have as a matter of design choice, depending on each particular case (see D1, claims 11-13; and Midoux *et al.,* column 3-16). Thus, in the absence of unexpected results, the claims are obvious variants of one another.

Thus, the claimed invention as a whole was *prima facie* obvious.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-15 of U.S. Patent No. 5,733,762, 3/1998, claims 9-15, and further in view of D3. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are readable on

a complex between at least one negatively charged nucleic acid and at least one positively charged polymeric conjugate bonded by electrostatic interaction. The polymeric conjugate contains a polymer of monomeric units with free NH3+ groups. The free NH3+ are substituted, with a ratio of at least 10%, by gluconyl based non-charge residues and do not bind to any recognition signal recognized by a cell membrane receptor.

The difference between Midoux and the subject matter of the present claimed invention is that the claimed invention is directed to histidine residues that are protonable in a weakly acidic medium and further comprise a functional group enabling them to be bound to the polymer while not being recognized by a cell membrane receptor. The objective of employing histidine residues or residues with an imidazole nucleus conjugated to polylysine, for example, is to enhance the protection of transfectinng nucleic acid from lysosomal decomposition following endocytosis.

However, at the time the invention was made, D3 describes the fusion-mediating properties of polyhistidine relative to liposomes. The concept of fusion is caused by the polycationic nature of polyhistidine having an acid pH, and to the combination of the polycation with membrane phospholipids that induces phase separation in the dual lipid layer (D3, abstract). D3 also indicates that the fusion-mediating behavior associated with polyhistidine having a low pH is more effective than the one associated with Ca2+ or polylysine. More specifically, D3 indicates that a charge ratio of only 0.2 or less between the polyhistidine and the liposome enables effective fusion to be ensured, whereas it must exceed 0.7 with Ca2+ and be of around 1 with polylysine (see page 4414, column 2, last sentence to page 4415, column 1, line 13; table IV). In addition and most importantly, D3 suggests that if the interaction between the hydrophobic segments of viral envelope glycoproteins is an important step in the fusion process, the protonation of the histidine residues of the viral protein with an acidic pH would be an alternative fusion means (page 4115, last paragraph).

It would have been obvious to one of ordinary skill in the art to incorporate histidine residues to any of the free NH3 groups of the polylysine in D1 in order to enhance the fusion and translocation of DNA complexed with polylysine. One of ordinary skill in the art would have been motivated to have incorporated histidine residues to any of the free NH3 groups of the polylysine in D1 because of the reasons set forth in the preceding paragraphs. Thus, the subject mater as claimed in this instant application, wherein histidine residues are incorporated to NH3+ groups of the

polylysine polymer, is obvious variants of the subject matter as recited in claims 9-15 of the '762 patent.

To the extent that the claims are readable on specific substitution ratios, and further optional incorporation of cell-recognition peptides, it would have been obvious to one of ordinary skill in the art as a matter of design choice to employ any ratio and/or well known cell recognition peptides in the polymeric complexes of Midoux taken with D3, particularly since such teachings are also disclosed in the claims of Midoux (claim 9).

To the extent that the claim are readable on recognition signals, the selection of nucleic acids and the selection of the defining parameters of the polymer, *e.g.,* the substitution ratio of the free NH3+ of the lysine units, the selection of the molecular weight of the nuclei acid and the average number of base pairs of the nucleic acid per monomeric unit molecule, are minor modification or options that a person of ordinary skill in the art would have been motivated to have as a matter of design choice, depending on each particular case (see claims 9-15). Thus, in the absence of unexpected results, the claims are obvious variants of one another.

Claims 11-15 are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dave Nguyen whose telephone number is 571-272-0731.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, may be reached at 571-272-0804.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is 703-305-8568.

DAVE T. NGUYEN
PRIMARY EXAMINER